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EXAMINER	
HICKEY,K	
ART UNIT	**PAPER NUMBER**
1635	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/765 244	Applicant(s) Seibel et al.	
	Examiner Karen Hickey	Group Art Unit 1635	9

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P ri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-61 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-61 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7, filed 4/20/99

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

DETAILED ACTION

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there are amino acid and nucleotide sequences disclosed in the drawings and the text of the specification which have not been submitted in computer readable format as required by the rules set forth in 37 CFR 1.821 through 1.825. Additionally, sequences should be assigned sequence ID numbers and should be identified using those numbers in the format SEQ ID NO: # when referred to in the specification, figure legends and claims.

A complete reply to this Office action must include compliance with this request.

Foreign patent document AA JP709976 cited on IDS 1449 filed July 20, 1999 has not been considered because no translation was provided.

Specification

The substitute specification voluntarily filed December 16, 1996 has not been entered because it does not conform to 37 CFR 1.125(b)because:

The substitute specification must be accompanied by: 1) a statement that the substitute

specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

A statement reading "This is a 371 of International Application No. PCT/DE95/00775, filed with the Patent Cooperation treaty on June 11,1995." or "This application is the National Stage filing of International Application No. PCT/DE95/00775 filed on June 11,1995." should be entered following the title of the invention or as the first sentence of the specification.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

It is noted that the substitute specification submitted does contain both the required priority statement and an abstract. If the applicant complies with 37 CFR 1.125(b) the substitute specification will be entered and these objections will be overcome.

If the applicant intends to resubmit the substitute specification in a manner that complies with 37 CFR 1.125(b), it should be noted that the specification as filed is replete with spelling and grammar errors. It is requested that the applicant correct such errors prior to resubmission. Additionally, the substitute specification begins with a Table of Contents which indexes sections of the application by page number. If the application were to issue as a patent, those page

numbers would no longer be relevant, as all references are made by column and line number in a U.S. patent. Although the examiner appreciates the inclusion of the Table of Contents, it should be deleted from the substitute specification prior to resubmission, since it is improper.

It is also noted that at the time this Office action was written, the substitute specification did not contain the translation of the "Summary of the Invention".

It is noted that the specification as filed, and in the substitute specification filed December 16, 1996, the section entitled "Summary of the Invention" has not been filed. Rather than this passage of the specification being present, applicants indicate in the specification that this passage has yet to be translated into English from the parent PCT, which is in German. Any disclosure which will be subsequently filed for this missing section of the specification will be considered at the time the second Official action is prepared. Such an action will be made final if all the rejections therein are repeated for the same reasons of record, even if a new rejection is added, but such new rejection is made because of the addition of the missing passage in the specification, since this was not available when the instant first Official action was prepared.

Drawings

The drawings are objected to because in figure 6b one axis is labeled in German. Correction is required.

Claim Objections

Claims 18 and 35 are objected to under 37 CFR 1.75(c), as being of improper dependent

form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 18 limits the peptide-nucleic acid chimera of claim 1 to one which "carries a cell-specific, compartment specific, or membrane-specific recognition signal". The same limitation is already included in independent claim 1, so claim 18 does not further limit claim 1.

Claim 35 recites a chimeric peptide-nucleic acid fragment with the binding site of a bidirectional transcriptional terminator, and is dependent on claim 34. Claim 34 recites a chimeric peptide-nucleic acid fragment with the binding site of a mitochondrial transcriptional terminator. The term "bidirectional terminator"appears to be of broader scope than the term "mitochondrial terminator", which might be included in the term "bidirectional terminator", therefore claim 35 does not further limit claim 34.

Claims 10, 11, 12, 13, 17 and 22 are objected to because of the following informalities: the term "grouping(s)" is used when the correct term would be "group(s)". Appropriate correction is required.

Claim 16 is objected to because of the following informalities: the word "to" is missing; the claim reads "gene be" instead of "gene to be". Appropriate correction is required.

Claim 21 is objected to because of the following informalities: the phrase "any one of" should have been removed when the claim was amended to be singly dependent. Appropriate correction is required.

Claim 25 is objected to because of the following informalities: the word "linked" is misspelled as "liked". Appropriate correction is required.

Claim 44 is objected to because of the following informalities: the word "phosphorylated" is inappropriately placed in parentheses. It is not clear whether the word is meant to be amended out of the claim, or if it is merely a typing error. Appropriate correction is required.

Claim 61 is objected to because it was amended improperly. When indicating the amendments made to the claim, an extra bracket was inserted, making it unclear what was removed and what was added to the claim. The extra bracket needs to be deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16, 17, 21, 26, 27, 29, 36, 39, 52 and 58-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10

USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance; claim 16 recites the broad recitation "promoter", and further recites the narrower recitation "preferably a mitochondrial promoter". It is unclear whether the claim is broadly drawn to any promoter, or if it is drawn only to a mitochondrial promoter.

Claim 17 recites the broad recitation "amino acid" , and the claim further recites the narrower recitation "preferably a lysine or cysteine". It is unclear whether the claim is drawn broadly to any amino acid, or if it is only drawn to a lysine or a cysteine.

Claim 21 recites the broad recitation "bifunctional linker", and the claim further recites the narrower recitation "preferably a heterobifunctional linker". It is unclear whether the claim is drawn broadly to any bifunctional linker or if it is only drawn to a heterobifunctional linker.

Claim 26 recites the broad recitation "promoter", and the claim further recites the narrower recitation "preferably a mitochondrial promoter" and the even narrower recitation "especially preferably a mitochondrial promoter of the light strand". It is unclear whether the claim is drawn to any promoter, a mitochondrial promoter or the mitochondrial promoter of the

light strand.

Claim 27 recites the broad recitation "transcription-regulatory sequences", and the claim further recites the narrower recitation "preferably mitochondrial transcription-regulatory sequences". It is unclear whether the claim is drawn broadly to any transcriptional regulatory sequences, or if it is only drawn to mitochondrial transcriptional regulatory sequences.

Claim 29 recites the broad recitation "binding site for the RNA synthesis apparatus", and the claim further recites the broad recitation "preferably the binding site for the mitochondrial transcription factor 1 and the mitochondrial RNA polymerase". It is unclear whether the claim is drawn broadly to any binding site for the RNA synthesis apparatus or only to the binding site for the mitochondrial transcription factor 1 and the mitochondrial RNA polymerase .

Claim 36 recites the broad recitation "mitochondrial replication origin", and the claim further recites the narrower recitation "preferably the replication origin of the heavy mt DNA strand". It is unclear whether the claim is drawn broadly to any mitochondrial replication origin or only to the replication origin of the heavy mt DNA strand.

Claim 39 recites the broad recitation "selection gene", and the claim further recites the narrow recitations "preferably an antibiotic resistance gene" and "preferably the oligomycin or chloramphenicol resistance gene". It is unclear whether the claim is drawn broadly to any selection gene or if it is drawn only to antibiotic resistance genes or only the oligomycin and chloramphenicol genes.

Claims 52 recites the broad recitation "overhanging ends", and the claim further recites

the narrow recitation "preferably 5' -overhanging ends". It is unclear whether the claim is drawn broadly to any type of overhanging end or if it is drawn only to 5'-overhanging ends.

Claims 1, 3, 4, 6, 7, 8, 10, 13, 14-17, 20, 22, 24, 25, 28, 29, 34-37, 41, 44-46, and 50-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

All the claims referenced above are drawn to a chimeric peptide-nucleic acid fragment. In general, the claims are grammatically unclear and it difficult to understand what is being claimed. In many of the claims, the choice made for the transitional phrase renders the scope of the claim ambiguous. Specifically see the following:

Claim 1 describes the peptide as linked "via the linking agent which via amino acids...is linked therewith". From the wording of the claim there is no indication of what the protein is linked to, although the assumption is that the claim is directed to a nucleic acid linked to the carboxyl terminal of a signal peptide. An alternative interpretation, however, might be that the chimera is linked to something else via the carboxyl terminal of the peptide portion of the chimera. Due to vague and indefinite wording, it is not possible to determine what chimeras are actually being claimed.

Claim 1 ends by stating the purpose of the linkage "as to ensure the appropriate nucleic acid introduction into cell organelles and cells". For the purposes of examination herein "appropriate... introduction" has been interpreted as meaning that the signal peptide would direct the nucleic acid to the target cell or organelle. As written, however, it is difficult to understand

what scope this is referring to, because grammatically it is poorly worded.

Claims 3, 4, 8, 17, 19, 25, 28, 29, 34, 35, 36, 44, 45, 46, 51 and 54 are rejected because of the use of the word "has, have or having". "Has, have and having" are considered to be open language, therefore the scope is indefinite, unless the specification as filed expressly defines has/have/having differently.

Claim 6 indicates the nucleic acid portion of the claimed chimera "may" hybridize with itself, and it "may" form sticky ends. The word "may" is indicating the capacity of the chimera to perform a conditional function, which is merely the recitation of a latent characteristic, the scope of which is unclear. Instead, the claim should definitively link the characteristic to the chimera by removing the word "may", ie. "wherein the nucleic acid hybridizes to itself and forms an overhanging 3' end".

The term "hybridize with itself" in claim 6 is a relative term which renders the claim indefinite. The term "hybridize with itself" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree nor does it provide conditions under which the hybridization would be expected to occur or under which one would assess whether or not a nucleic acid hybridizes to itself. Because the term "hybridizes with itself" is indefinite, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. One cannot determine from the specification what nucleic acids are encompassed by the claim because there is no definition indicating the degree of hybridization required.

Claim 7 describes the nucleic acid component of the chimera as being "ribonucleic acid,

preferably deoxyribonucleic acid". It is unclear whether the claim is drawn to RNA, DNA or both.

Claim 10 describes the reactive linkage group of the chimera as containing an " amino function when the linkage agent contains an amino-reactive grouping". The use of the word "when" in this claim leaves the scope of the claim undefined because it can not be determined what is being claimed when the linkage agent does not contain an "amino-reactive grouping". Therefore, it cannot be determined what chimeras are encompassed by this claim.

Claim 12 is indefinite because of the use of the word "preferably". The claim describes the attachment of the linking group as being a C2-spacer, but preferably a C6-spacer. It is unclear what length spacer the claimed linker should have, therefore it cannot be determined what chimeras are encompassed by this claim.

Claim 13 is drawn to a peptide-nucleic acid chimera with a linking group. The claim describes the linking group as being located "at the 3' hydroxy/phosphate terminus or the 5' hydroxy/phosphate terminus of the nucleic acid, but preferably at the base". It is unclear where the linking group of the claimed molecule is located, in particular, the word "preferably" makes the claim indefinite as to whether the linkage group is required to be at a base or whether it should be at a terminal phosphate or hydroxy group. Therefore, it cannot be determined what chimeras are encompassed by this claim.

Claim 14 indicates the type of nucleic acids linked to peptides which are being claimed. It is unclear what the scope of the claim is because the types of nucleic acids are listed using the

conjunctions "or" and "and/or". Alternative expressions are allowed in claims as long as they present no uncertainty or ambiguity with respect to scope or the clarity of claims. The language of claim 14 is unclear as to what combinations of items are being claimed. It is assumed for the purposes of examination herein that the applicant is claiming a chimera with the nucleic acid component being any one of the listed type of nucleic acid, linked to the peptide at either the 5' or the 3' end of the nucleic acid. As written, however, the claim could be interpreted to include chimeras wherein the nucleic acid component consists of the listed components linked together, either at the 3' end or the 5' end, or both, or even that one of the listed nucleic acids is linked to the peptide with both the 3' end and the 5' end. Therefore, it cannot be determined what chimeras are encompassed by this claim.

Claim 20 is drawn to a peptide-nucleic acid chimera where the peptide component is the ornithine transcarbamylase signal peptide extended "by an artificial cysteine". The specification does not define an "artificial" cysteine, nor is there any indication of how the cysteine in the claimed molecule is distinguished from a natural cysteine. So, therefore, there is no way to determine what cysteine the applicant intends to claim.

Claim 22 describes the linking group of the chimera as containing thiol "and/or" amino reactive groups "when" the nucleic acid and peptide "carry" thiol "and/or" amino reactive groups. The use of the word "when" in this claim leaves the scope of the claim undefined because it can not be determined what is being claimed when the linking group does not contain thiol and/or amino reactive groups. Additionally, the use of "and/or" makes the scope of the claim unclear.

Although there are a finite number of combinations for the thiol and amino groups, it can not be determine from the claim which combinations are being claimed, ie. is there a requirement for the groups to correspond between the linker to the nucleic acid or peptide, or could there be thiols on the linker, but amino groups on the nucleic acid . The claim indicates there is a correspondence between the linking groups, but it is not clear what that correspondence is. Therefore it cannot be determined what chimeras are encompassed by this claim.

Claim 24 indicates the claimed chimera "can" overcome membranes. The word "can" is indicating the capacity of the chimera to perform a conditional function, which is merely the recitation of a latent characteristic, the scope of which is unclear. Instead, the claim should definitively link the characteristic to the chimera by removing the word "can", ie. "wherein the molecule overcomes membranes".

Claim 31 is drawn to a peptide nucleic acid chimera which is under transcriptional control by elements of mitochondrial H and L strand transcription control. The specification discusses a variety of transcriptional control elements from the mitochondrial H and L strand, including promoters, polymerase binding sites and terminators. It is unclear from this claim whether the nucleic acid portion of the chimera is required to have all the required elements for transcriptional control from the mitochondrial H and L strands, or if some or one of the mitochondrial control elements need to be present, possible combined with control elements of a different system. It is unclear what chimeras this claim would encompass.

Claims 32 and 36 are drawn to a peptide-nucleic acid chimera under transcriptional

control by the mitochondrial transcriptional control element 'conserved sequence blocks'. Claims 32 and 36 refer to the 'conserved sequence blocks' as being derived from the mitochondrial light strand or heavy strand, respectively, and it is unclear whether the claims are referring to the same sequences or if the sequences are different.

Claim 35 is indefinite with respect to scope because of the use of the word "preferably". It is unclear whether the scope of the claim is limited to binding sites for bidirectionally acting termination factor binding sequences or if the claim encompasses all termination factor binding sequences and the bidirectionally acting termination factor binding sequence is meant as an example. Therefore, it cannot be determined what chimeras are encompassed by this claim.

Claim 41 is indefinite with respect to scope because of the use of the word "preferably". It is unclear whether the scope of the claim is limited to a multiple cloning site with restriction sites that do not occur anywhere else in the plasmid, or if the claim also encompasses multiple cloning sites containing restriction sites which do occur elsewhere in the plasmid. Therefore it cannot be determined what chimeras are encompassed by this claim.

Claims 30, 42, and 43 utilize the terms "arranged in the 3' direction", "arranged in the 5' direction", or "in the 5' direction" referring to the relative position of nucleotide sequences within the nucleic acid fragment of the chimera claimed in claim 25. Claim 25, however, states that the nucleic acid fragment is circularized, so the relative positions of all sequences could be described as being 5' or 3', the relative distance would just be different. The placement of the sequences referred to is unclear, so it is not possible to determine what molecules are encompassed by the

claim.

Claim 44 indicates the nucleic acid portion of the claimed chimera has ends "capable" of ligation. The word "capable of" is indicating the capacity of the chimera to perform a conditional function, which is merely the recitation of a latent characteristic, the scope of which is unclear.

Claim 45 recites the limitation "the nucleic acid fragment has 'blunt ends' or overhanging 3' ends, preferably 5' ends" in the last line of the claim. Due to the dependence on claim 25, the nucleic acid claimed in claim 45 already has the limitation that the nucleic acid fragment is "cyclized at both ends", which has been interpreted as a circular nucleic acid. Because the nucleic acid claimed in claim 45 is circular, it is difficult to understand how it would be possible to apply limitations to the ends of the nucleic acid fragment, as ends should not exist. Therefore, it cannot be determined what chimeras are being claimed.

Claim 46 recites the limitation "the nucleic acid fragment has 4 nucleotides comprising 5' overhangs" in the third line of the claim. Due to the dependence on claim 25, the nucleic acid claimed in claim 46 already has the limitation that the nucleic acid is "cyclized at both ends", which has been interpreted to mean that the nucleic acid is circular. Because the claimed nucleic acid is circular, it is difficult to image how it would be possible for the nucleic acid fragment to have an overhanging end. Therefore, it cannot be determined what chimeras are being claimed.

Claim 50 is indefinite with respect to scope because of the use of the word "preferably". It is unclear whether the claimed peptide-nucleic acid chimera is required to have a modified nucleotide in the 'loop' or if the claim is meant to encompass any peptide-nucleic acid chimera

with a modified nucleotide. Therefore it cannot be determined what chimeras are encompassed by this claim. Claim 50 is also indefinite because it recites the limitation "the loop" at the end of the claim. There is insufficient antecedent basis for this limitation in the claim, because it is referring to claim 25, which does not mention a loop.

Claim 51 is indefinite because of the use of the word "preferably". It is unclear whether the claim is limited to oligonucleotides with restriction sites that do not occur "in a non-repeated fashion" in the plasmid, or if the claim also encompasses oligonucleotides which contain restriction sites which are "repeated" in the plasmid. Therefore, it cannot be determined what chimeras are encompassed by this claim.

Claim 52 is indefinite because of the use of the word "preferably". It is unclear whether the nucleic acid portion of the peptide-nucleic acid chimera being claimed is required to have a cleavage site localized outside of the recognition sequence, or if the cleavage site could be located anywhere in the nucleic acid. Therefore, it cannot be determined what chimeras are encompassed by this claim.

Claim 57 recites the limitation "the DNA" in the second line of the claim. There is insufficient antecedent basis for this limitation in the claim, because it is dependent on claim 56, which recites any nucleic acid.

Claims 60 and 61 are vague and indefinite because they recite a method of use of the claimed nucleic acid-peptide chimera "for the introduction into" cells, but the claim does not state what is being introduced into cells. Based on prior claims, the assumption is that the method is

meant to introduce specific nucleic acids, or the chimera into cells, but unless that is stated as such, it cannot be determined what the claimed method actually is.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "plasmid" in claims 25, 33, 37, 39, 40, 41 and 51 is used by the claim to mean "double stranded DNA with terminal covalent cross-links," while the accepted meaning is "double stranded circular DNA capable of self-replication." The specification explicitly states (p. 8) that the invention would not function if the nucleic acid portion of the chimera were a double stranded circular plasmid, but describing the invention using the word "plasmid" would suggest such an embodiment for the invention. By using the term "plasmid" to describe the nucleic acid component of the claimed chimera one skilled in the art would envision the invention differently than the applicants intended, as such, one would interpret the claimed invention as something entirely different.

Claims 58-61 provide for the use of the chimerical peptide-nucleic acid fragment of claim 1 or 25, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 58-61 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a

process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Although the applicants appear to be claiming a method, the preamble does not actually state a method. The claims 58-61 recite the desired outcome of the process, introducing nucleic acids into cells and organelles, but the claims are actually drawn to the process itself. A process is defined by the steps of the process, but in claims 58-61 there are no steps presented which would define the claimed processes. Because the claimed processes are not defined, the claims are indefinite, as one skilled in the art would not know what the processes are.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 18, 19 and 25 are drawn to a peptide-nucleic acid chimera made up of a nucleic acid linked to a signal peptide. The peptide portion of the chimera is described as a signal sequence which is "cell-specific, compartment-specific, or membrane-specific". The specification

describes one signal peptide, the mitochondrial matrix-specific signal sequence from ornithine transcarbamylase, but the claim reads broadly on any signal peptide, the rest of which have not been described by name or by amino acid sequence in the specification.

Claim 14 is drawn to a peptide-nucleic acid chimera wherein the nucleic acid component of the chimera is referred to as "defined nucleic acids, antisense oligonucleotides, messenger RNA's or transcribable and/or replicatable genes". This claim reads broadly on any nucleic acid and it cannot be determined from the specification what nucleotides are being claimed by structure, ie. nucleotide sequence. In particular, the claim reads on antisense oligonucleotides, but the specification does not name genes that would be targeted by the claimed antisense chimeras nor is there a description of any specific antisense molecules and the structure of such cannot be *a priori* predicted.

Claims 32 and 36 are drawn to a peptide nucleic acid chimera which is under transcriptional control by the 'conserved sequence blocks' of the mitochondrial trancription control element. The 'conserved sequence blocks' are not defined by structure, ie. nucleotide sequence in the specification. Therefore, it cannot be determined what the 'conserved sequence blocks' are.

Claim 37 is drawn to a peptide nucleic acid chimera, wherein the nucleic acid portion of the chimera is a plasmid containing a regulatory sequence. The specification does not define regulatory sequence by structure, ie. nucleotide sequence, and it cannot be determined from the specification what nucleic acids would be encompassed by this claim.

Claim 38 is drawn to a peptide nucleic acid chimera, wherein the nucleic acid portion of the chimera is a plasmid containing the mitochondrial replication regulatory motif. The specification does not define the mitochondrial replication regulatory motif by structure, ie. nucleotide sequence, and it cannot be determined from the specification what nucleic acids, by structure (ie. nucleotide sequence) would be encompassed by this claim.

Claims 1 and 58-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using one specific type of peptide-nucleic acid chimera for the in vitro delivery of a nucleic acid to the mitochondria, does not reasonably provide enablement for methods of use of that peptide-nucleic acid to deliver a nucleic acid to the mitochondria *in vivo*, nor does it reasonably provide enablement for the use of peptide-nucleic acid chimeras to deliver any nucleic acid to any cell or any organelle *in vivo* or *in vitro*. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 58-61 are drawn to methods of using the claimed nuclei acid-peptide chimera, and its embodiments, to introduce the nucleic acid component into cells and cell compartments, specifically eukaryotic cells. Claim 1 is drawn to a peptide-nucleic acid chimera wherein the peptide component is a signal peptide. Although claim 1 is not stated as a method claim, it is written using active language, "as to ensure the appropriate nucleic acid introduction", and would also need to be enabled in the specification.

Claims 1 and 58-61 recite no context for the claimed methods and would read on *in vivo* (whole organism) applications. The specification does not teach methods of using the claimed nucleic acid-peptide chimeras *in vivo* (whole organism) because it does not provide any guidance for practicing the claimed methods *in vivo* (whole organism). The specification does not provide any guidance for the use of peptide-nucleic acid chimeras *in vivo* (whole organism) with respect to what cells or organelles to target, how to target specific cells or organelles, what mode and composition to use to deliver the peptide-nucleic acid chimera, and how much of the peptide-nucleic acid chimera to administer. The specification teaches the 'particle gun' system, microinjection, electroporation and lipotransfection as modes to deliver the claimed peptide-nucleic acid chimeras, but none of these modes would be applicable for *in vivo* (whole organism) delivery.

The specification does not present any evidence to suggest that a nucleic acid has been delivered *in vivo* using the constuct of claim 1 or the methods of claims 58-61 and does not provide guidelines for doing such. Nor does the the field to date have any general guidelines for *in vivo* (whole organism) delivery of nucleic acids to cells or organelles using signal peptides. As such, it would require trial and error and undue experimentation for one skilled in the art to practice the methods of claims 58-61 or make the construct of claim 1 for *in vivo* (whole organism) applications.

Claims 1 and 58-61 read broadly on practicing these methods to introduce any nucleic acid-signal peptide chimera into any cell or cell compartment. The specification discloses only

two types of signal peptides, the ornithine transcarbamylase signal peptide, which is specific for importation into mitochondrial matrix, and the KDEL peptide, which is specific for importation into the endoplasmic reticulum. The specification does not teach, either directly or by reference to art, representative signal sequences for a variety of cell and organelle types. Reciting two examples is not considered to provide adequate support for one skilled in the art to envisage utilizing the claimed methods over the broad breadth claimed.

Each cellular transport mechanism requires different features in the recognized signal peptide. In order to utilize cellular transport one would need to know how many residues of the signal peptide are needed, whether either terminal amino acid needs to be exposed, what amino acid residues could be crosslinked to the nucleic acid and whether the structure of the signal peptide would be adversely altered if a nucleic acid were crosslinked with the carboxyl terminus. The specification provides no guidance with respect to signal peptide features required for cell transport, beyond teaching the requirements for the ornithine transcarbamylase signal peptide, and provides no guidance on how to determine such. Determination of signal peptide features required for cell transport would need to be done *de novo* for every signal peptide. As such, it would require trial and error and undue experimentation for one skilled in the art to make the construct of claim 1 or to utilize the methods in claims 58-61 commesurate with the scope of these claims.

Claims 1 and 58-61 recite signal peptide-nucleic acid chimeras wherein the link between the signal peptide and the nucleic acid is at the carboxyl terminus of the peptide. This reads

broadly on any signal peptide, except the KDEL sequence, which would include signal peptides that require residues at or near the carboxyl terminus to be accessible during importation. The specification provides no guidance on how one skilled in the art could crosslink such a signal peptide at the carboxyl terminus while maintaining its ability to utilize cellular transport mechanisms. As such, it would not be possible for one skilled in the art to make the construct of claim 1 or utilize the methods in claims 58-61 wherein the signal peptide component of the chimera has essential features at its carboxyl terminus.

The specification teaches that the nucleic acid is double stranded, but also has the diameter of a single stranded molecule and is linked linearly with the signal peptide, which results in a chimera with a size and shape compatible with the membrane transport mechanism. Claims 1 and 58-61, however, read broadly on a peptide-nucleic acid chimera wherein the nucleic acid component can be any oligonucleotide. Oligonucleotides encompassed by these claims would include those nucleic acids with a bulky tertiary structure or highly charged nucleic acids, which may not be compatible with cellular transport mechanisms. The specification provides no guidance on what nucleic acids would be compatible with specific cellular transport mechanisms and does not provide guidance on how to determine such. Further, the specification provides no guidance on how to utilize the claimed methods with a bulky or highly charged nucleic acids.

The specification provides guidance on practicing the claimed methods to introduce nucleic acid-peptide chimeras into the mitochondria, *in vitro*, utilizing the ornithine transcarbamylase signal peptide linked to a double stranded DNA with covalently cross-linked

ends. Claims 1 and 58-61, however, read on practicing the claimed methods for any signal peptide (except the KDEL sequence) linked a the carboxyl terminus to any nucleic acid to introduce a nucleic acid into any cell or organelle, *in vivo* or *in vitro*. The specification does not provide guidance sufficient to practice the methods of claims 58-61or make the construct of claim 1 commensurate in scope with these claims. Nor does the field have general guidelines which would allow one skilled in the art to make and/or use the claimed invention over such broad range.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-24 and 54-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Lin et al.

Claims 1-24 and 54-61 are drawn to a nucleic acid-peptide chimera wherein the peptide component is a signal peptide and the chimera is designed to utilize cellular transport mechanisms to deliver the nucleic acid to a target cell or organelle and methods thereof. The claims require the nucleic acid to be linked to the signal peptide at the carboxyl terminus, and exclude the signal peptide sequence KDEL.

Lin et al. teach delivering a nucleic acid into the interior of cells by chemically linking it to an importation competent signal peptide at the carboxyl terminus of the signal peptide (see col 3 line 66 to col 4 line 1 and col 7 lines 38-41 and 66 to col 8 line 1). Additionally, Lin et al. teach methods for importing such a molecule into a cell (see claims 1 and 3). Thus Lin et al. anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-24 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin

et al. as applied to claims 1-24 and 58-61 above, in view of Horwich et al. and Latham et al.

Claims 1-24 and 58-61 are drawn to a nucleic acid linked to the carboxyl terminus of a signal peptide, which facilitates transport of the nucleic acid across a membrane to a target organelle or cell. Embodiments of the invention being claimed include nucleic acid components with features which include the ornithine transcarbamylase signal sequence, promoters, termination sequences, expressible genes, phosphorothiotae backbones, and multiple cloning sequences.

As stated above, Lin et al. teach delivering a nucleic acid into the interior of cells by chemically linking it to an importation competent signal peptide at the carboxyl terminus of the signal peptide (see col 3 line 66 to col 4 line 1 and col 7 lines 38-41 and 66 to col 8 line 1). Additionally, Lin et al. teach methods for importing such a molecule into a cell (see claims 1 and 3). Lin et al. also teach the specific embodiments of claim 1 which are claimed in claims 2 (nucleic acid with more than two bases), 3 (a nucleic acid with secondary structure), 7 (RNA or DNA), and 18 (recognition signal). However, Lin et al. do not teach all of the embodiments of the peptide-nucleic acid chimera of claim 1.

Latham et al. teach other embodiments of claim 1, which are claimed in claims 8 (phosphorothioate linkages), 9 (reactive linkage group on the nucleic acid), 11 (thiol linkages), 13 (linkage at the 3' end, 5' end or base of the nucleic acid), 14 (nucleic acid is antisense, mRNA, or transribed genes), 15 (phosphorothioate), 16 (promoter), 17 (Cys or Lys at the carboxyl terminus), 19 (peptidase claevage site), and 21(bi or hetero functional crosslinker). Latham et al.

teach that these embodiments of claim 1 would be useful because to improve the stability of the nucleic acid, allow genes to be expressed after reaching a target cell, or it would allow a nucleic acid to be separated from the transport peptide after reaching the target.

The embodiments of claim 1 have been taught in prior art, and it would have been obvious to one skilled in the art to incorporate the disclosed modifications into the composition of claim 1 as follows:

Claim 2 is drawn to the composition of claim 1 wherein the nucleic acid component of the chimera is at least two bases. Latham et al. (p 11, lines 1-6) teach that it would be useful to utilize a nucleic acid conjugate, including a peptide chimera, to deliver nucleotides of a length from 8-30 nucleotides for antisense purposes.

Claim 7 is drawn to the composition of claim 1 wherein the nucleic acid component of the chimera is either RNA or DNA. Latham et al. (p 20, lines 29-30) suggest conjugates including DNA or RNA.

Claim 8 is drawn to the composition of claim 7 wherein the nucleic acid component of the chimera has a phosphorothioate backbone. Latham et al. (p8, line 8) suggest conjugates with phosphorothioate modified nucleotides to increase the stability of the nucleotide.

Claim 9 is drawn to the composition of claim 1 wherein the nucleic acid component of the chimera has a "reactive linkage group". Latham et al. (p18-20) suggest conjugates with a linker group with a free thiol group, which can react to form a disulphide bond in order to link the oligonucleotide to the transport agent. It would be obvious to one skilled in the art to place a

reactive group on the nucleic acid of the chimera to provide a means to link the nucleic acid to the linker and, in turn, link it to the peptide.

Claim 11 is drawn to the composition of claim 1 wherein the linkage group of the chimera has a thiol and the linker also has a thiol. Latham et al. (p2, line 19 to p3, line 10) discuss directly and through examples in the art nucleic acid-peptide conjugates linked by a disulphide bond. It would have been obviuos to one skilled in the art to incorporate reactive thiols into the linker and into the linkage group in order to form a disulphide bond, linking the components to form the chimera.

Claim 19 is drawn to the composition of claim 1 wherein the peptide component of the chimera has a peptidase cleavage site. Latham et al. at numerous points suggest a conjugate in which the nucleotide and the transport agent are separated during or after transport across the membrane. On p5, lines 2-5, Latham et al. explicitly suggest the separation occur by cleavage by proteolytic enzymes at the target area. It would have been obvious to one skilled in the art to incorporate a peptidase cleavage site into the composition of claim 1 in order to separate the nucleic acid from the protein once the nucleic acid was at target area.

Claim 21 is drawn to the composition of claim 1 wherein the linkage agent of the chimera is a heterofunctional or bifunctional cross-linker. Latham et al. (p19, line 21 to p20, line 10) teach using a bifunctional linker, and also teach a bifunctional linker capable of reacting simultaneously with proteins or nucleic acids, which would qualify as a heterobifunctional cross-linker. It would have been obvious to one skilled in the art to use a bifunctional or heterofunctional linker to join

the nucleic acid and peptide of claim 1.

Horwich et al., 1985, teach the amino acid residues residues of the ornithine transcarbamylase signal peptide which are important for transport into the mitochondria. It would have been obvious to incorporate the ornithine transcarbamylase signal sequence into a signal peptide-nucleic acid chimera as disclosed by Lin et al.

One would have been motivated to design a signal peptide-nucleic acid chimera as described in claim 1 because Lin et al. disclose such a construct and describe how it could be used for delivery of nucleic acid based drugs. It would have been obvious to link the nucleic acid to the signal peptide at the carboxyl terminus of the peptide because Lin et al. disclose such a link. Many of the embodiments of the peptide-nucleic acid chimera claimed would have been obvious, because they have been disclosed by Latham et al. as beneficial embodiments of a signal peptide-nucleic acid chimera, like that disclosed by Lin et al., which would be useful for delivering nucleic acid based drugs to a target cell or organelle. Therefore, the invention as a whole, as claimed in claims 1-24 and 58-61 would have been obvious to one skilled in the art at the time the invention was made.

Any inquiry concerning this communication should be directed to Karen A. Hickey at telephone number (703)308-7523.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliot can be reached at (703) 308-4003. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Hickey
September 13, 1999